Basis of derivation of EPA RfC for methyl bromide (MeBr)

Critical Studies: Reuzel et al. (1987): Chronic (29-month) inhalation toxicity and carcinogenicity study of methyl bromide in rats. Report No. V86.469/221044. Netherlands Organization of Applied Scientific Research, Division for Nutrition and Food Research, TNO.EPA/OTS Document No. 86-8700001202.

Reuzel et al. (1991): Chronic inhalation toxicity and carcinogenicity study of methyl bromide in Wistar rats. *Food and Chemical Toxicology* 29(1):31-39.

DESCRIPTION OF REUZEL et al. STUDIES:

Animals and dosing

- 50 male and 50 female Wistar rats per dosage group
- 10 male and 10 female Wistar rats per satellite group
- 4 dosage groups: 0, 3, 30, or 90 ppm 98.8% pure MeBr
    - Measured by GC every 30 minutes
- 6 hr/day, 5 days/week for up to 29 months (approximate lifespan)
    - Males exposed 128 weeks; females exposed 129 weeks)

Testing protocol

- 4 satellite groups of 10 animals/sex/exposure level
    - Sacrificed at 14, 53, and 105 weeks of exposure
    - Urine analyses, hematology, and clinical chemistry conducted at 12-14 weeks and 52-53 weeks
    - Necropsy exam of 11 organs and 36 tissues
        - Entire respiratory tree (incl. trachea, larynx lungs)
        - Cross-sections of nose, heart, brain, adrenal glands
- All animals observed daily
- Body weights recorded weekly for 12 weeks
    - Monthly thereafter

Effects (compared with controls)

- At 90 ppm
  - Increased mortality in males at 114 weeks and females at 121 weeks
  - Decreased bw gains in both sexes
  - Decreased mean absolute brain weight in females
    - Without changes in histology or behavior
  - Decreased absolute kidney weight in males and females
  - Hyperkeratosis (thickening of outer epidermal layer) of esophagus of males at 29 months
  - Heart lesions in males and females
    - Believed to contribute to the increased mortality observed at this exposure concentration
  - Moderately severe degenerative changes in olfactory and mid-nasal epithelium at 29 months (dose-dependent)

- At 30 ppm
  - Decreased absolute kidney weight in females
  - Decreased relative kidney weight in males
  - Degenerative changes in olfactory and mid-nasal epithelium at 29 months

- At 3 ppm
  - Very slight hyperplasia of basal cells, with degeneration of olfactory epithelium in dorso-medial part of nasal cavity
  - No other statistically significant histopathologic, hematologic, or clinical chemistry changes
  - **LOAEL** of 3 ppm based upon above nasal changes [dosimetric adjustment used to calculate human equivalent concentration (**HEC**) of **0.12 ppm**]

Derivation of RfC

- LOAEL (HEC) of 0.12 ppm (for mild nasal lesions) divided by uncertainty factors
- Uncertainty factors of
  - 10 for intra-species variability (*i.e.*, variability within the human population)
  - 3 for the use of an LOAEL for mild effects
  - 3 for interspecies (rat to human) variability because dosimetric adjustments have

been applied to determine an HEC

- 10 x 3 x 3 = 100 (3 x 3 = 10)
- **RfC = 1.3 ppb** (based on 0.005 mg/m^3 x 0.25 for converting from mg/m^3 to ppm)
    - 0.005 x 0.25 = 0.00125 ppm = 1.25 ppb, rounded to 1.3 ppb